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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,350	10/01/2003	Ursula Schindler	02481.1655-01	3812

22852 7590 12/14/2004

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EXAMINER	
TRUONG, TAMTHOM NGO	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 12/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/674,350	SCHINDLER ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,20,21 and 27-34* is/are rejected.

7)☒ Claim(s) *12-19 and 22-26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment of 10-13-04 has been full considered. The amended claims have overcome the previous 112/2nd paragraph by deleting one of the two formula I's. However, new issues of indefiniteness are noted, and new references are found which raise the following new ground(s) of rejection. Therefore, the finality of the previous action is withdrawn herein.

Claims 1-10 have been cancelled.

Claims 11-34 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 29 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

   a. Claim 29 recites "A method for activating at least one soluble guanylate cyclase...", which is unclear if a treatment or a bioassay is claimed. If a treatment is intended, it is unclear what disease is treated.

   b. Claim 30 recites "A method for treating at least one disorder associated with a disturbed cGMP balance...", which is unclear what the intended disease is.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Scope of Enablement:** Claims 29, 30 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of hypertension, stroke, angina pectoris, or myocardial infarct, does not reasonably provide enablement for the treatment of other diseases such as: atherosclerosis, thrombosis, bronchial asthma, chronic renal insufficiency, diabetes, liver cirrhosis, etc.. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims:

Claim 29 recites "A method for activating at least one soluble guanylate cyclase..." which is not specific to the treatment of any disease, but at the same time, encompasses the treatment of just about every disease known in the art because guanylate cyclase is an enzyme that is involved in virtually every cellular process.

Claim 30 recites "A method for treating at least one disorder associated with a disturbed cGMP balance..." Again, no specific treatment is recited. A disorder associated with a disturbed cGMP can read on any disorder because cGMP is involved with many receptors' responses, and is the basic component of cellular response.

Claim 34 recites the treatment of many disorders including endothelial dysfunction, diastolic dysfunction, atherosclerosis, thrombosis, restenosis, cardiac insufficiency, pulmonary hypertension, erectile dysfunction, bronchial asthma, chronic renal insufficiency, diabetes, and liver cirrhosis, and improving restricted learning capacity and memory power...All of which may or may not be related to cGMP or guanylate cyclase.

Therefore, the scope of claims 29, 30, and 34 covers the treatment of a wide range of diseases that are not practical in a clinical setting.

The amount of direction or guidance presented: The specification only provides data for 14 compounds that can activate soluble guanylate cyclase. While such activity can warrant the treatment of hypertension, stroke, angina pectoris, or myocardial infarct, it does not have any correlation to the treatment of atherosclerosis, thrombosis, chronic renal insufficiency, diabetes,

liver cirrhosis, improving learning capacity or memory power. Many of these disease have underlying factors that are not related to guanylate cyclase, or additional factors. For example, atherosclerosis is caused by plagues of cholesterol, lipids, and cellular debris built up in the inner layer of the artery wall, thus, the most effective treatment is reducing such plaque. Clearly, activating guanylate cyclase would not treat atherosclerosis. Likewise, thrombosis is related to Factor X of the blood coagulation pathway, and not related to guanylate cyclase. Similarly, diabetes is related to the availability of insulin, or the production of glycogen while chronic renal insufficiency and liver cirrhosis have other factors such as: alcohol consumption, hepatitis, and drug induced factor. Regarding improving learning capacity and memory power, there is nothing in the specification that would guide the skilled clinician to apply the claimed compounds for such a use.

Thus, merely showing the activation of guanylate cyclase for 14 compounds does not sufficiently guide the skilled clinician to treat the many disorders recited or embraced by the instant claims.

The state of the prior art: Currently in the art, the drugs that treat hypertension, do not treat atherosclerosis while the cholesterol lowering agents can reduce atherosclerosis, but do not treat hypertension. Likwise, none of the anti-diabetic agents can treat hypertension, atherosclerosis, thrombosis, etc. In other words, there is no single agent that can treat the many diseases of different etiologies.

The relative skill of those in the art: Even with the high level skill of those in the art such as physician and Ph. D., to treat the many diseases encompassed by the instant claims, one

would have to carry out a pharmacokinetic profile for each of the claimed compound, and establish a therapeutic index as well as LD_{50} for each of them. Such a task requires more than routine experimentation.

The predictability or unpredictability of the art and **the quantity of experimentation necessary**: It is well known that the pharmaceutical art is unpredictable because each disease manifests differently. Therefore, to treat the many diseases encompassed by the instant claims using a large number of compounds, it would require undue experimentation since no single agent can treat diseases of different etiologies.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 11, 20, 21, and 28 rejected under 35 U.S.C. 102(b) as being anticipated by **Taniguchi et. al.** (JP 10-87492 – see also CAS printout). On page 11, Taniguchi et. al. disclose a tetrahydro-quinazoline compound (the third compound on column 20) that reads on the instant formula I with the following substituents:

i. One of R^1 and R^2 is an alkyl group substituted by an alkoxy;

ii. The other of R^1 and R^2 is hydrogen;

iii. R^3 is a heteroaryl group (included in the definition of "aryl").

The disclosed compound also has pharmaceutical use and thus, the claimed pharmaceutical composition is also anticipated by the teaching of Taniguchi et. al.

4. Claims 11, 20, 21, and 28-34 are rejected under 35 U.S.C. 102(b) as being anticipated by **Lee et. al.** (US 5,436,233; US 5,439,895; EP 579,496 A1). In Example 6(cc), Lee et. al. disclose a tetrahydro-quinazoline compound that reads on the instant formula I with the following substituents:

i. One of R^1 and R^2 is an alkyl group substituted by an alkoxy;

ii. The other of R^1 and R^2 is hydrogen;

iii. R^3 is a heteroaryl group (included in the definition of "aryl").

The disclosed compound can inhibit cGMP-PDE, or TXA_2 synthase, and thus, the claimed pharmaceutical composition is also anticipated by the teaching of Lee et. al. Also, the method claims 29-34 are anticipated as well because the disclosed compound can treat hypertension, angina, myocardial infarction, etc.

5. Claims 11, 20, 21, 27 and 28 rejected under 35 U.S.C. 102(b) as being anticipated by **Giencke et. al.** (US 5,250,530 or EP 407,899 A2). In Table A, Giencke et. al. disclose several tetrahydro-quinazoline compounds (e.g., compound #8.4, 101.9, 102.29, 102.30) that read on the instant formula I with the following substituents:

i. One of R^1 and R^2 is an unsubstituted alkyl group;

ii. The other of R^1 and R^2 is hydrogen;

iii. R^3 is a heteroaryl group (included in the definition of "aryl").

Note, in the reference, when R^5 and R^6 together form $-(CH_2)_4-$, then the pyrimidinyl ring becomes a *tetrahydro-quinazolinyl* ring.

The disclosed compound also has fungicidal property, and thus, the claimed pharmaceutical composition is also anticipated by the teaching of Giencke et. al.

Also, on column 4 of US'530, Giencke et al disclose a process of making said compounds which involves starting materials that are similar to those recited in the instant claim 27. Therefore, the process claim is anticipated as well.

6. Claims 11, 20, 21, and 28 rejected under 35 U.S.C. 102(b) as being anticipated by **Albrecht et. al.** (CA 86:29739 – see CAS printout). Albrecht et. al. disclose several tetrahydro-quinazoline compounds that read on the instant formula I with the following substituents:

i. One of R^1 and R^2 is an unsubstituted alkyl group,

ii. The other of R^1 and R^2 is hydrogen;

iii. R^3 is a heteroaryl group (included in the definition of "aryl").

The disclosed compound also has pharmaceutical use and thus, the claimed pharmaceutical composition is also anticipated by the teaching of Albrecht et. al.

Claim Objections

7. Claims 12-19, and 22-26 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The prior arts of record do not read on compounds of the

instant formula I in which one of R^1 and R^2 is a cycloalkyl group, or R^3 is a substituted phenyl group.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M-F (10:00-6:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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12-03-04

Tamthom N. Truong
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